VOLUME XVII December 1961 NUMBER 12

Clinical Proceedings

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CLINICAL PROCEEDINGS

OF CHILDREN'S HOSPITAL OF THE DISTRICT OF COLUMBIA

2125 13th Street, N.W., Washington 9, D. C.

PUBLISHED MONTHLY BY THE STAFF AND RESEARCH FOUNDATION OF CHILDREN'S HOSPITAL, WASHINGTON, D. C.

Cases are selected from the weekly conferences held each Thursday at 12:00 noon, from the Clinicopathological conferences and from weekly Staff meetings.

This bulletin is printed for the benefit of the present and former members of the Attending and Resident Staffs, and the clinical clerks of Georgetown and George Washington Universities.

Subscription rate is $3.00 per year. Those interested make checks payable to "Clinical Proceedings Dept.," Children's Hospital, Washington, D. C. Please notify on change of address.

Second-class postage paid at Washington, D. C.

Clinical Proceedings

CHILDREN'S HOSPITAL WASHINGTON, D.C.

VOLUME XVII • DECEMBER 1961 • NUMBER 12

Amino-Aciduria in Infancy and Childhood*

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The study of normal biochemical and physiological phenomena is usually a necessary prerequisite for the elucidation of disease processes. It is also true that the study of pathological states has afforded valuable information leading to the understanding of normal processes. This has been especially true in the field of amino-acid metabolism.

The excess excretion of amino acids may result from deranged intermediary metabolism in various organs or from impaired renal tubular reabsorption. These defects may be inherited or acquired. Dent and Walshe[1] have classified the amino-acidurias into "overflow" and "renal" types. Many metabolic studies have been done to determine normal values of alpha-amino nitrogen excretion and individual amino-acid excretion from infancy to adulthood.[2-6] Normal children excrete 2.0 to 4.0 mg. of alpha-amino nitrogen per Kg. of body weight per day.[7] In full term and premature infants up to 6 months of age urinary alpha-amino nitrogen levels may exceed 6.0 mg. per Kg. per day normally, but after this period levels remain around 2.0 mg. per Kg. per day throughout childhood.[8] In patients with amino-aciduria urinary excretion may exceed normal values by tenfold to twentyfold. Diet has been shown to exert relatively little influence upon the amount of alpha-amino nitrogen in the urine.[2, 9]

Over the past decade there has been an increasing interest in detection of free amino acids in the urine of patients with varied disorders. Newer and more accurate chromatographic techniques have made these studies possible as a routine laboratory procedure.[10-16] Recently, loading techniques have been utilized to determine the ability of enzyme systems to carry out specific biochemical reactions and have contributed considerably

* This material has been reviewed by the Office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.

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to the field of medical genetics.[17, 18] Rational therapeutic approaches have been applied in phenylketonuria and galactosemia.

Chisolm[19] and Paine[20] have recently published excellent reviews of the amino-acidurias. Although survey studies have been numerous, the number of reported cases has been small. Such studies may shed new light on metabolic disorders and their mechanisms of production and thus stimulate new chemotherapeutic approaches toward their solution. After the present study began, Ghadimi and Shwachman[21] reported one of considerable size and discussed the principles of paper chromatography. The purpose of the present study is to evaluate urinary alpha-amino nitrogen excretion and chromatographic patterns in infants and children with such conditions as "failure to thrive," seizure disorders, mental retardation, repeated infections, renal and hepatic disorders, accidental poisoning, and other obscure or ill-defined disorders. All cases were observed on the Pediatric Service of Walter Reed General Hospital. A new syndrome[22] has been described, and amino-aciduria occurring in patients with gasoline and salicylate intoxication has been studied for the first time.[23]

MATERIALS AND METHODS

Fifty-five subjects who ranged in age from 4 weeks to 33 years were evaluated; there were 80 determinations of 24 hour urinary alpha-amino nitrogen excretion, as well as measurements of individual amino-acid excretion by paper chromatography. Specimen collection began at 6 A. M. and terminated at 6 A. M. the following day except for patients with acute intoxications and convulsions; urine collection from the latter groups started upon admission to the hospital and continued for 24 hours. Twenty cubic centimeters of NHCl was added to each specimen to insure sterility and prevent further chemical breakdown of urinary constituents. Specimens were placed in a freezer until analyzed. Kekki's method for copper determination of alpha-amino nitrogen was used.[24] Initially the paper chromatographic method of Oreskes and Saifer for amino acid screening was used.[13] For the last three months of the study preliminary chromatography of the native urine was performed, following the procedure of Ghadimi and Shwachman.[15] Color development of the chromatographs was by the Moffat and Lytle[6] and Rosen[12] stains. Standards were made for individual amino acids, using the method of Levy and Chung.[11]

RESULTS AND COMMENTS

Forty-seven patients suspected of having alteration of amino-acid metabolism and eight healthy controls comprise this study to date. Determinations were repeated several times in some individuals. The results have been expressed as the amount of alpha-amino nitrogen excretion per Kg.

TABLE 1

All Determinations

Patient	Diagnosis	Age	Wt. in Kg.	Date	24 hr. urine vol. in cc.	Total α-amino nitrogen mg/24 hr.	α-Amino nitrogen mg/Kg/B. W./24 hr.
1. D. B.	Malnutrition	1 6/12	8.5	3–15–60	340	110	12.9
2. R. A.	Cerebral cortical atrophy	6 wks.	4.8	2–9–60	200	84	17.5
		2/12	5.0	3–1–60	180	28	5.6
		5/12	6.4	6–24–60	240	11.1	1.7
3. L. B.	Congenital macrocephaly, hydrophthalmos, glaucoma, hypotonia, mental and growth retardation	6/12	5.9	2–29–60	200	48	8.1
		7/12	6.3	3–4–60	170	63	10.0
		7/12	6.3	3–21–60	270	60	9.5
		7/12	6.4	3–25–60	270	61.3	9.7
4. C. H.	Congenital obstructive uropathy, pyelonephritis	11/12	5.9	3–10–60	225	22.5	3.8
5. P. G.	Ataxia, telangiectasia	10	30.0	3–17–60	700	75	2.5
6. J. H.	Multiple congenital anomalies	1 4/12	6.8	3–23–60	170	29	4.3
		1 6/12	7.9	5–3–60	250	27	3.4
7. V. P.	Infectious hepatitis, acute yellow atrophy	6 wks.	3.6	3–20–60	Renal failure, tyrosine crystals in urine		
8. W. M.	Healthy	3/12	4.0	3–20–60	108	13.1	3.5
9. J. T.	Salicylate intoxication	2 5/12	14.5	4–1–60	650	244	16.8
			14.5	4–2–60	770	182	12.6
10. D. J.	Celiac syndrome	1 3/12	5.9	4–2–60	130	26	4.4
11. D. E.	Healthy	8/12	5.5	4–18–60	105	22.1	4.0
12. S. R.	Failure to thrive, ABO incompatibility, icterus neonatorum, exchange transfusion	4/12	4.2	4–21–60	105	39	9.2
		5/12	4.8	5–4–60	140	31.7	6.6
13. P. D.	Gasoline ingestion	2	10.0	4–22–60	300	83.6	8.4
14. L. W.	Healthy	8/12	5.2	4–25–60	240	10	1.9
15. K. A.	Cortical atrophy, microgyri	10 9/12	5.9	4–26–60	105	23	3.9
16. C. L.	Salicylate intoxication	3	13.6	4–27–60	1210	340	25.0
17. B. L.	Healthy	2	9.6	4–27–60	360	23.8	2.5
18. J. S.	Congenital toxoplasmosis	3/12	3.9	5–3–60	325	39	10.0
19. E. G.	Superficial oral lye burn	3	13.7	5–5–60	560	35.3	2.6
20. J. H.	Convulsive disorder, cerebral and cerebellar atrophy	3 5/12	16.4	5–7–60	390	113	6.9
				5–8–60	230	33.3	2.0
				6–1–60	255	19	1.1

TABLE 1—*continued*

Patient	Diagnosis	Age	Wt. in Kg.	Date	24 hr. urine vol. in cc.	Total α-amino nitrogen mg/24 hr.	α-amino nitrogen mg/Kg/B. W./24 hr.
21. S. H.	Neonatal omphalitis, portal hypertension, splenorenal and portacaval shunts	7	30.0	5-10-60	2200	321	10.7
				5-12-60	1220	311	10.3
				6-7-60	2240	354	11.8
22. D. R.	Cerebral cortical atrophy, convulsive disorder	5/12	6.8	5-10-60	240	88	12.9
				5-11-60	270	39.6	5.8
23. C. P.	Leukemia, terminal	10	27.7	5-10-60	1450	320	11.5
				5-11-60	1425	480	17.3
24. J. N.	Healthy	13/12	11.4	5-17-60	820	32.2	2.9
25. C. E. P.	Failure to thrive due to repeated illnesses	3/12	2.6	5-18-60	280	32.2	12.4
26. R. B.	Congenital obstructive uropathy, pyelonephritis, right nephrectomy	2/12	3.2	5-20-60	420	20.8	6.5
		5/12	5.5	8-3-60	800	32.1	5.8
27. A. C.	Healthy	27/12	14.8	5-20-60	370	67.0	4.5
28. A. B.	Healthy	33	60.9	6-3-60	2500	130	2.1
29. D. D.	Growth and mental retardation, hypotonia, no convulsions	10/12	5.5	5-1-60	120	39	7.1
30. W. K.	Leukemia, early	3	13.6	6-5-60	700	71	5.2
31. D. M. B.	Left facial hemiatrophy, convulsive disorder	3/12	4.6	6-8-60	155	5.3	1.2
32. A. S.	Hepatosplenomegaly, hypertension, hyperglobulinemia	7	17.7	6-7-60	550	27	1.5
				6-9-60	605	47	2.7
33. D. H.	Acute glomerulonephritis	5	16.4	6-10-60	1290	71	4.3
			16.0	6-16-60	1000	162	10.1
34. A. L.	Mongolism, mental retardation, congenital dislocated hips, fracture right femur	9/12	5.9	6-17-60	500	48	8.1
35. R. M.	Lead encephalopathy	11 1/12	10.0	6-20-60	440	31	3.1
			10.0	6-27-60	1200	59	5.9
			10.0	7-9-60	500	107	10.7
			10.0	7-13-60	800	202	20.2
36. W. R.	Pseudohypertrophic muscular dystrophy	5	17.3	6-23-60	300	46	2.7
				6-24-60	320	66	3.8
37. D. M. B.	Hypsarrhythmia	7/12	9.6	6-24-60	475	26	2.7

TABLE 1—*continued*

Patient	Diagnosis	Age	Wt. in Kg.	Date	24 hr. urine vol. in cc.	Total α-amino nitrogen mg./24 hr.	α-amino nitrogen mg/Kg/B. W./24 hr.
38. N. M.	Accelerated growth, mental retardation, hypertelorism	2 1/12	15.9	6-27-60	550	32	2.0
				6-28-60	450	55	3.4
39. C. S.	Leukemia, remission	2	10.5	7-25-60	150	28.7	2.7
40. R. M. S.	Ataxia, telangiectasia	6	14.4	7-25-60	400	43.9	3.1
41. M. R.	Prolonged physiologic jaundice, dehydration	4 wks.	3.2	7-29-60	180	28.4	8.9
42. J. K.	Hodgkin's disease, terminal	11	39.1	8-4-60	750	251	6.4
43. V. A. S.	Ataxia, telangiectasia	3	14.6	8-4-60	425	73.9	5.1
44. G. H.	Patent ductus arteriosus, interventricular septal defect, pulmonary effusion, postirradiation	5/12	4.7	8-4-60	350	66.9	14.2
45. B. R. P.	Xanthomatous granuloma of the calvarium	5	16.8	8-8-60	370	42.9	2.6
46. V. G.	Healthy	1 7/12	14.6	8-10-60	408	52	3.6
47. A. P.	Dwarfism	4	12.6	8-25-60	250	45.3	3.6
48. D. J.	Mongolism, congenital heart disease	5/12	4.4	8-26-60	200	23	5.2
49. K. McK.	Lysol ingestion	3	12.7	8-6-60	700	45.6	3.6
				8-9-60	700	45.0	3.5
50. C. M.	Grand mal seizures	10	28.6	9-6-60	400	111	3.8
				9-7-60	500	109	3.8
51. B. L.	Failure to thrive, malnutrition, mental retardation	11 1/12	9.3	9-9-60	600	82	8.8
			10.4	9-30-60	500	47	4.5
52. N. S.	Lead intoxication, mild	1 5/12	10.5	9-9-60	250	28.7	2.7
				9-23-60	300	46.2	4.4
53. E. M.	Granuloma of the anterior mediastinum	3	10.7	9-27-60	275	128	11.9
54. C. J.	Acute glomerulonephritis	3 6/12	17.5	10-17-60	1200	151	8.6
55. C. M.	Failure to thrive, progeria-like	6/12	3.0	4-16-60	90	10	3.3

of body weight. Creatinine and total nitrogen determinations were purposely omitted since recent work has shown that these values are quite variable.[2, 25] Urinary volume, total alpha-amino nitrogen excretion and amount of alpha-amino nitrogen per Kg. of body weight are listed in table 1. The

mean value of alpha-amino nitrogen excretion per Kg. of body weight per 24 hours, as well as the observed range and standard deviation were calculated for both controls and those with disease. In the control group the mean value was 3.1 mg. per Kg. per 24 hours, with a range of 1.9 to 4.5. The total study group mean was 6.7 mg. per Kg. per 24 hours with a range of 1.1 to 25.0 mg. per Kg. per 24 hours (table 2). These values correspond to those of other studies.[2, 24]

Patients with convulsive disorders are grouped in table 3. One-half the patients demonstrated hyperamino-aciduria; these patients all had pneumo-

TABLE 2

α-Amino Nitrogen Excretion

mg/Kg/B.W./24 hr.

8 Control determinations	
Mean	3.1
Range	1.9–4.5
Standard deviation	0.9
80 Whole group determinations in 55 patients	
Mean	6.7
Range	1.1–25.0
Standard deviation	4.8

TABLE 3

Convulsive Disorders

Patient	Diagnosis	Age	Wt. in Kg.	Date	α-Amino nitrogen mg/Kg./ 24 hours	Amino-acid pattern demonstrated by chromatography
2. R. A.	Cerebral cortical atrophy	6 wk.	4.8	2–9–60	17.5	Normal pattern, increased amounts
		2/12	5.0	3–1–60	5.6	
		5/12	6.4	6–24–60	1.7	
20. J. H.	Cerebral and cerebellar atrophy, convulsive disorder	3 5/12	16.4	5–7–60	6.9	Normal pattern, increased amounts
				5–8–60	2.0	
		3 9/12	16.4	6–1–60	1.1	
22. D. R.	Cerebral cortical atrophy, convulsive disorder	8/12	6.8	5–10–60	12.9	Glycine prominent
				5–11–60	5.8	Glycine prominent
31. D.M.B.	Left facial hemiatrophy, convulsive disorder	3/12	4.6	6–8–60	1.2	Normal pattern
37. D.M.B.	Hypsarrhythmia	7/12	9.6	6–24–60	2.7	Normal pattern
50. C. M.	Grand mal seizures	10	28.6	9–6–60	3.8	Normal pattern
				9–7–60	3.8	

encephalographic evidence of cortical atrophy and exhibited the highest excretion rates of urinary alpha-amino nitrogen in the 24 hour period following seizures. Amino-acid paper chromatography in this group revealed a prominence of urinary excretion of glycine, serine, histidine and glutamine. Patient 22 had a very prominent glycine distribution. Figure 1 depicts the amino-acid excretion during the day following seizures and subsequently.

Four patients with renal and three with hepatic disturbances are shown in table 4. A rise in excretion of amino acids in a patient with acute glomerulonephritis is depicted in figure 2; no gross alteration of paper chromatographic amino-acid pattern was noted. Three patients with hepatic disorders demonstrated amino-aciduria. Patient 7 expired of renal failure three days following onset of jaundice at age 6 weeks; tyrosine crystals could be seen in the original urine specimen. Elevation of urinary amino acids was noted particularly in patients 12 and 21 who had neonatal jaundice. In patient 21, a generalized hepatic disturbance was indicated by the usual laboratory liver function tests, and urinary paper chromatography showed prominence of cystine, histidine, glycine, glutamic acid, and alanine.

Amino-aciduria was found in four of seven patients with accidental poisoning (table 5). The progressive amino-aciduria found in a patient with lead encephalopathy is demonstrated in figure 3. The highest level of

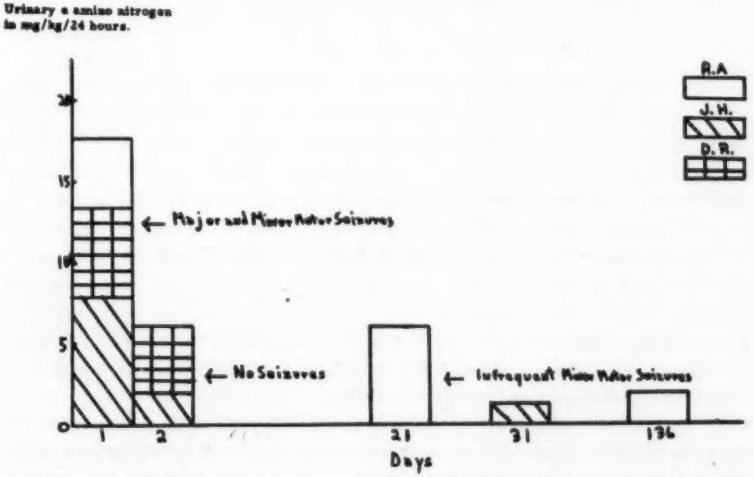


FIG. 1. Urinary α amino nitrogen excretion in mg/Kg/24 hours on the day of seizures and subsequently.

TABLE 4

Renal and Hepatic Disorders

Patient	Diagnosis	Age	Wt. in Kg.	Date	α-Amino nitrogen mg/Kg./24 hours	Amino-acid pattern demonstrated by chromatography
4. C. H.	Congenital obstructive uropathy, pyelonephritis	1 1/12	5.9	3-10-60	3.8	
7. V. P.	Infectious hepatitis, acute yellow atrophy, renal failure	6 wk.	3.6	—	—	Tyrosine
12. S. R.	Failure to thrive, ABO erythroblastosis fetalis, exchange transfusion	4/12	4.2	4-21-60	9.2	Normal pattern, increased amounts
		5/12	4.8	5-4-60	6.6	Normal pattern
21. S. H.	Neonatal omphalitis, portal hypertension, splenorenal and portacaval shunts	7	30.0	5-10-60	10.7	Prominence of cystine, histidine, glycine, glutamic acid, alanine
26. R. B.	Congenital obstructive uropathy, pyelonephritis, right nephrectomy	2/12	3.2	5-20-60	6.5	Normal pattern
		5/12	5.5	8-3-60	5.8	
33. D. H.	Acute glomerulonephritis	5	16.4	6-10-60	4.3	Normal pattern
			16.0	6-16-60	10.1	Normal pattern, increased amounts
54. C. J.	Acute glomerulonephritis	3 6/12	17.5	10-17-60	8.6	Aspartic acid, glycine, serine, alanine

alpha-amino nitrogen excretion recorded in this study was found in a patient with salicylate intoxication (case C. L., fig. 4). A urinary chromatographic pattern of increased cystine, histidine, lysine, serine, methionine, tyrosine and glutamine was seen in both patients with this disorder. Figure 5 shows chromatograph stain densities of a patient with salicylate intoxication compared with those of a control patient. There was no elevation of urinary amino acids as a result of tissue necrosis due to lye and lysol ingestion observed in patients 19 and 49.

Patients with a diagnosis of "failure to thrive" represent a large group of patients studied. Table 6 shows the excretion values of alpha-amino nitrogen for some of these patients. Patient 51 excreted large amounts of cystine and alanine, but study of the bone marrow and slit lamp examina-

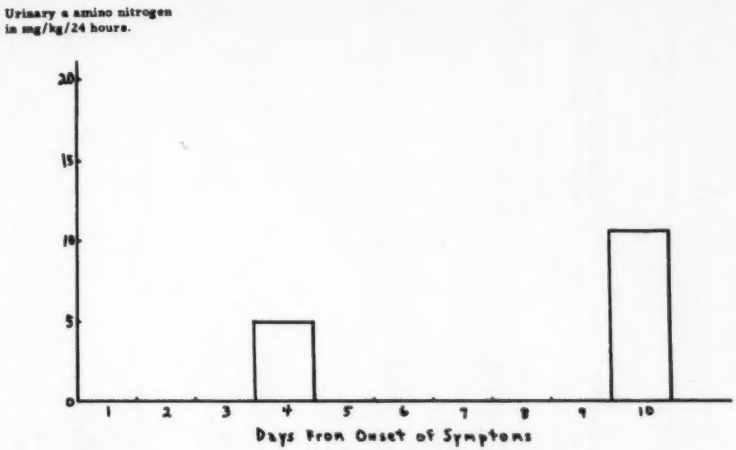


FIG. 2. Urinary α amino nitrogen excretion in mg/Kg/24 hours in a patient with acute glomerulonephritis.

tion of the lens did not reveal cystine crystals. Unfortunately, follow-up studies were not performed on patients 1 and 25 who showed rapid clinical improvement and weight gain following hospitalization.

Other subjects exhibiting some degree of amino-aciduria are listed in table 7. Patients in the active and remission stages of leukemia are depicted in figure 6.

DISCUSSION

Amino-aciduria is the term applied to the excess excretion of amino acids in the urine. Values exceeding 5 mg. per Kg. per day of alpha-amino nitrogen in this study are considered to represent amino-aciduria. The amino-acidurias have been classified by Ghadimi and Shwachman[21] into those due to both physiological and pathological conditions (table 8). This follows closely the classification of Dent and Walshe.[1] Numerical values following the disease entities represent the number of patients from the present study.

Types of Pathological Amino-Aciduria

Overflow Amino-Aciduria—Acquired

In liver disease increased plasma and urinary levels of amino acids are to be expected.[26, 27] In biliary obstruction, erythroblastosis fetalis and hepatitis faulty de-amination occur, and in acute yellow atrophy, autolysis takes place. Tyrosine and cystine excretion is prominent in patients with acute yellow atrophy and offers a poor prognosis. Where protein catabolism is prominent, amino-aciduria is to be expected. Jonxis and Huisman[28]

TABLE 5

Accidental Poisoning

Patient	Diagnosis	Age	Wt. in Kg.	Date	Toxic substance in blood and urine	α-Amino nitrogen mg./Kg. /24 hr.	Amino-acid pattern as demonstrated by chromatography
9. J. T.	Salicylate intoxication	2 5/12	14.5		Blood salicylate		Cystine, histidine plus lysine, serine plus glutamine
				4–1–60	59.2 mg/100 ml.	16.8	
				4–2–60	42.0 mg/100 ml.	12.6	
13. P. D.	Gasoline ingestion	2	10.0	4–22–60		8.4	Generalized increase
16. C. L.	Salicylate intoxication	3	13.6		Blood salicylate		Cystine, histidine plus lysine, serine plus glutamine
				4–27–60	43.2 mg/100 ml.	25.0	
				4–28–60	30.0 mg/100 ml.		
19. E. G.	Superficial oral lye burn	3	13.7	5–5–60		2.6	
35. R. M.	Lead encephalopathy	1 11/12	10.0	6–20–60	Urine lead	3.1	Generalized increase
					Before EDTA		
					7–3–60		
					.48 mg./100 ml.		
				6–27–60		5.9	
					7–5–60		
					.58 mg./100 ml.		
					After EDTA		
				7–9–60		10.7	
					7–9–60		
					.05 mg./100 ml.		
				7–13–60		20.2	
					7–25–60		
					.08 mg./100 ml.		
49. K. McK.	Lysol ingestion	3	12.7	8–6–60		3.5	
				8–9–60		3.8	
52. N. S.	Lead intoxication	1 5/12	10.5	9–9–60	Urine lead	2.7	Normal pattern
					Before EDTA		
					9–17–60		
					.40 mg./100 ml.		
					After EDTA		
				9–23–60		4.4	
					9–26–60		
					.05 mg./100 ml.		

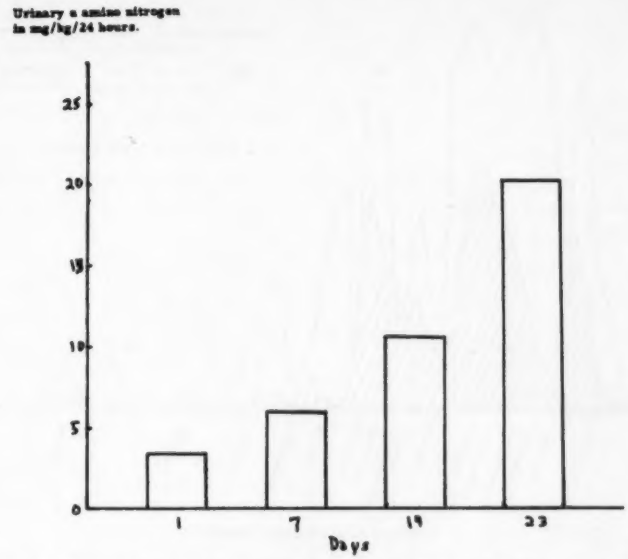


FIG. 3. Urinary α amino nitrogen in a patient with lead encephalopathy

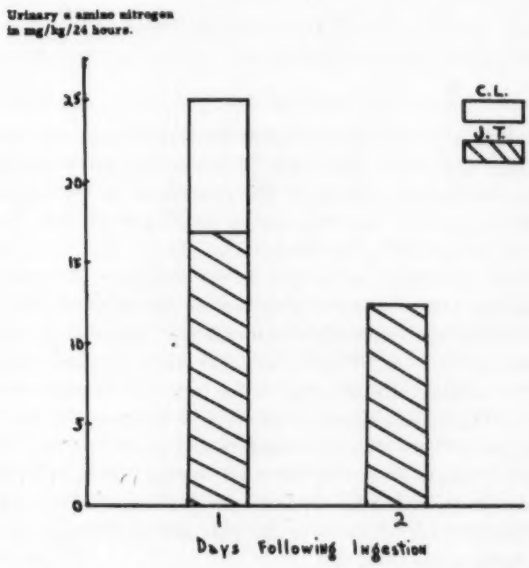


FIG. 4. Urinary α amino nitrogen excretion in salicylate intoxication

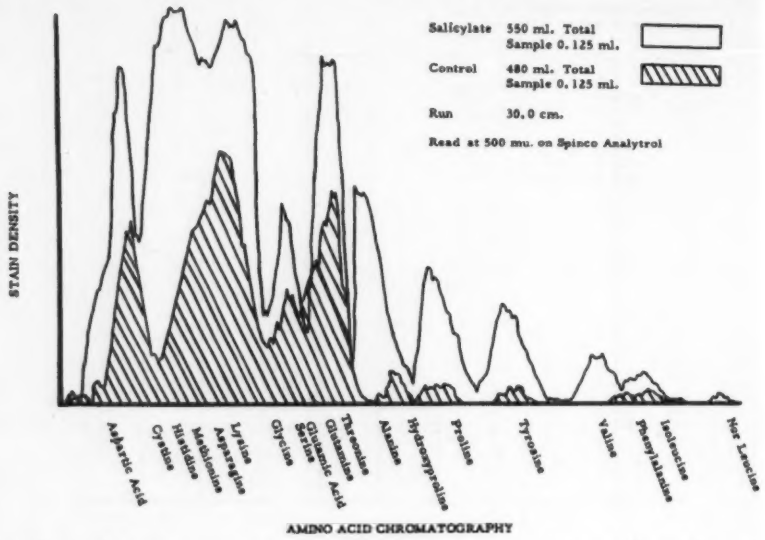


FIG. 5. Urinary amino acid paper chromatography in a patient with salicylate intoxication and in a control.

and Eckhardt and Davidson[29] have demonstrated an increased excretion following infusion of protein hydrolysate.

Overflow Amino-Aciduria—Congenital

Phenylketonuria is a hereditary disorder transmitted by a single autosomal recessive gene.[30] A deficiency of phenylalanine hydroxylase is responsible for the accumulation of phenylalanine in the plasma and its excretion in the urine;[17] this enzyme is necessary for the conversion of phenylalanine to tyrosine. The mental deficiency associated with phenylketonuria is felt by many to be due to the formation of organic acids or amines resulting from the de-amination or decarboxylation of phenylalanine.[31] The typical child has fair hair and skin, blue eyes, mental retardation and usually eczema. Twenty-five per cent of these patients have seizures.[17] The mental outlook is said to be improved if a low phenylalanine diet is begun early in life although cases have been reported in which the patient escaped severe mental retardation without dietary control.[32, 33] Diagnosis can be made by noting the color change produced by the addition of ferric chloride to the urine. Despite the testing of the urine of several thousand infants in our clinic over the past two years, no new case of the disease has been uncovered.

TABLE 6

Failure to Thrive

Patient	Diagnosis	Age	Wt. in Kg.	Date	α-Amino nitrogen mg./Kg./ 24 hours	Amino-acid pattern as demonstrated by chromatography
1. D. B.	Malnutrition	1 5/12	8.5	3-15-60	12.9	Normal pattern, increased amounts
15. K. A.	Growth and mental retardation, cataracts, hypotonia, no convulsions	1 9/12	5.9	4-26-60	3.9	
25. C. E. P.	Failure to thrive due to repeated illnesses	3/12	2.6	5-18-60	12.4	Glycine, serine, histidine, glutamic acid
29. D. D.	Growth and mental retardation, hypotonia, no convulsions	1 9/12	5.5	5-1-60	7.1	Normal pattern
47. A. P.	Dwarfism	4	12.6	8-25-60	3.6	
51. B. L.	Failure to thrive, malnutrition, mental retardation	1 11/12	9.3	9-9-60	8.8	Cystine, alanine
			10.4	9-30-60	4.5	
55. C. M.	Failure to thrive, progeria-like	6/12	3.0	4-16-60	3.3	

Smith and Strang[34] recently reported a baby girl with mental deficiency, unpleasant smelling urine, intermittent generalized pitting edema, and decreased muscle tone who, in addition, had excess urinary excretion of alpha-hydroxy-butyric acid, phenylpyruvic acid and acetic acid. Cystathioninuria has been described in an elderly imbecile by Harris;[35] excess cystathionine was found in the liver and kidney, and feeding methionine led to an increased excretion of cystathionine. Allan et al.[36] and Westall[37] have observed l-arginino-succinic acid in the spinal fluid, plasma and urine of two mentally deficient siblings. This amino acid is an intermediate in the urea cycle, but it is not known whether the condition is due to an enzymatic metabolic block or is a more complex disorder since the spinal fluid level of arginino-succinic acid is greater than the plasma level. Childs and Cooke[38] have described an infant with mental retardation, episodic vomiting, thrombocytopenia, and neutropenia with hyperglycemia and glycinuria. In the present study, one patient with cerebral atrophy also demonstrated hyperglycinuria. Current studies are being made to classify her disorder.

TABLE 7

Miscellaneous

Patient	Diagnosis	Age	Wt. in Kg.	Date	α-Amino nitrogen mg./Kg/24 hours	Amino-acid pattern as demonstrated by chromatography
3. L. B.	Congenital macrocephaly, hydrophthalmos, glaucoma, hypotonia, mental and growth retardation	5/12	5.9	2-20-60	8.1	Generalized increase
		7/12	6.3	3-4-60	10.0	
		7/12	6.3	3-21-60	9.5	
		7/12	6.4	3-25-60	9.7	
18. J. S.	Congenital toxoplasmosis	3/12	3.9	5-3-60	10.0	Generalized increase
23. C. P.	Leukemia, terminal	10	27.7	5-10-60	11.5	Generalized increase
				5-11-60	17.3	
34. A. L.	Mongolism, mental retardation, congenital dislocated hips, fracture right femur	9/12	5.9	6-17-60	8.1	
42. J. K.	Hodgkin's disease, terminal	11	39.1	8-4-60	6.4	Generalized increase
44. G. H.	Patent ductus arteriosus, interventricular septal defect, pulmonary effusion, postirradiation	9/12	4.7	8-4-60	14.2	Glutamic acid prominent

There are conflicting reports by prominent investigators concerning the presence or absence of amino-aciduria in idiopathic hypoproteinemia.[7, 39, 40] We have not studied patients with this problem.

Maple syrup disease[41] is characterized by the excretion of urine with a pleasant maple syrup-like odor in infants who exhibit early onset of spasticity, myoclonic seizures, and rapid progression to decerebrate rigidity and death. The keto acids, leucine, isoleucine and valine have been demonstrated in the urine of these patients, in whom the defect is believed to be a block in carboxylation.[42, 43]

Renal Amino-Aciduria (Normal Blood Level)—Acquired

Children with rickets have been shown by Jonxis and Huisman[44] to excrete excessive amounts of a limited number of amino acids; some are excreted in the free form and others in a form from which they can be set free by acid hydrolysis. These free and combined acids are lysine, histidine, glycine plus alanine, glutamic acid, and threonine plus serine. Vitamin D therapy reduces the amount of urinary amino acids in these patients but does not always return their values to normal levels.

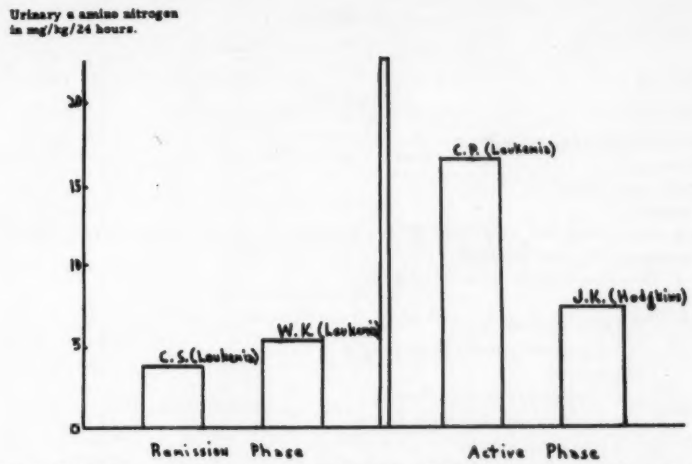


FIG. 6. Urinary α amino nitrogen excretion in mg/Kg/24 hours in patients with leukemia and Hodgkin's disease.

Darkening of the urine together with a disturbance of the metabolism of tyrosine and phenylalanine in scorbutic patients has been known for a long time.[45] Jonxis and Huisman[45] found reversible amino-aciduria in infants with scurvy who were treated for three or more weeks with ascorbic acid.

In patients in whom tissue breakdown occurs (radiation therapy, or thermal or chemical burns) gross amino-aciduria may be expected, and is related to the severity of the tissue damage and total area of the body involved.[46-48] Chisolm[19] places these entities among the unclassified group of amino-acidurias. There may be an important renal tubular effect as well as local tissue wasting.

Amino-aciduria is found to accompany the nephrotic syndrome.[49, 50] Woolf and Giles[50] have observed amino-aciduria in 25 of 29 patients; 16 of 29 also had glycosuria. On bidimensional chromatography, free urinary amino acids migrated into patterns which resembled "H" and "R" configurations. The "R" pattern was associated with a poor prognosis. Prominent amino acids in this pattern were proline, leucine, valine and alanine. In the "H" pattern, β-amino-isobutyric acid, taurine, tyrosine, leucine and valine were prominent. One of our patients with acute glomerulonephritis had an accompanying amino-aciduria with prominent excretion of aspartic acid, glycine, serine and alanine. Another patient had elevated urinary amino acids with a normal pattern of excretion. Further investigation should continue since so few patients with this condition have been studied for amino-aciduria.

TABLE 8

Classification of Amino-Aciduria

(Modified from Ghadimi and Shwachman,[21] with numbers indicating patients in this study)

Physiological Amino-Aciduria
- Prematurity
- Neonatal period
- Pregnancy
- β-Amino isobutyric acid (BAIB) and glycinuria (5% of a certain population)

Pathological Amino-Aciduria

I. Overflow (hyperamino-acidemia)
- Acquired
  - Liver disease (3)
  - Infusion of protein hydrolysate
- Congenital
  - Phenylpyruvic oligophrenia
  - α-hydroxy-butyricaciduria
  - Cystathioninuria
  - Allan's disease (argininosuccinicaciduria)
  - Idiopathic acute hypoproteinemia
  - Maple syrup disease
  - Glycinemia

II. Renal (normal blood levels)
- Acquired
  - Rickets
  - Scurvy
  - Burns
  - Nephrotic syndrome (2)
  - Poisoning—Lead (2)
    - Uranium
    - Lysol (1)
    - Gasoline (1)
    - Salicylate (2)
  - Leukemia in childhood (3)
  - Kwashiorkor
  - Post convulsion (3)
  - Miscellaneous—Tyrosiluria in premature infants with low ascorbic acid in diet
    - Irradiation (1)
    - Severe infection (2)
- Congenital
  - Glycophosphoamino-aciduria ± cystinosis
  - Vitamin D-resistant rickets
  - Familial glycoamino-aciduria
  - Cystinuria
  - Glycinuria
  - Hepatolenticular degeneration
  - Galactosemia
  - Hartnup disease
  - Lowe's disease

TABLE 8.—*continued*

Amino-aciduria associated with mental deficiency (7)	
Miscellaneous—	Gargoylism
	Muscular dystrophy
	Arthrogryposis
	Erythroblastosis fetalis (1)
	Progeria
	Diabetes mellitus
	Familial recurrent pancreatitis
	Sensitivity to excess of vitamin D
	Celiac syndrome
	Hypoplastic anemia
Macrocephaly, hydropthalmos, glaucoma, mental retardation, hypotonia (1)	

Children with lead poisoning have been found to exhibit a triad of hypophosphatemia, amino-aciduria and glycosuria; in less severe cases only amino-aciduria is observed.[51, 52] Recently Chisolm et al.[53] have reported the above triad plus rickets in a patient with lead intoxication. Our patient with lead encephalopathy demonstrated increasing amino-aciduria after hospitalization, but does not have rickets at present. Uranium, cadmium and mercury poisoning have been known to produce amino-aciduria.[54, 55] Metal poisoning is felt to cause amino-aciduria by producing renal tubular lesions or causing disturbance of renal tubular enzyme systems.[53] Our patient with Lysol ingestion did not exhibit the amino-aciduria previously described by Spencer and Franglen.[56] Amino-aciduria has accompanied gasoline ingestion in one patient in this study. This patient has been followed for six months and has had no subsequent ill effects. There was no specific pattern of amino-aciduria which would reveal a hepatic or renal origin.

The highest levels of urinary alpha-amino nitrogen excretion in this study were recorded in two patients with salicylate intoxication. Both blood and urinary salicylate levels were high, and the prothrombin time was decreased. In each patient, urinary amino-acid chromatographic patterns revealed excessive excretion of cystine, histidine, lysine, serine, methionine, tyrosine and glutamine. It has been recently shown that salicylate increases oxygen consumption and uncouples oxidative phosphorylation[57-60] by preventing the conversion of adenosine-di-phosphate to adenosine-tri-phosphate. Glycogenolysis is accelerated[61] while glycogen synthesis by the liver is inhibited.[62] Hyperglycemia has been noted in both experimental and clinical salicylate poisoning.[63, 64] Fatty acid catabolism and the production of ketone bodies by the liver can be related to these defects or to a more specific enzyme defect in the Krebs tricarboxylic acid cycle.[65, 66] It is postulated that the amino-aciduria in salicylate intoxica-

tion is caused by the defective production of high-energy phosphate bonds due to uncoupling of oxidative phosphorylation in the body tissues. This metabolic function is necessary for protein synthesis, and almost all known proteins contain amino acid-carbohydrate-phosphate linkage. An alternate explanation is that the amino-aciduria could be due to renal tubular enzyme inhibition. Further studies are under way to elucidate this mechanism and will be reported subsequently.[23]

In patients with leukemia and other neoplastic diseases amino-aciduria can be expected to occur in the acute phase; this is demonstrated in two of our patients. Ghadimi and Shwachman[21] mention leukemia in their classification of amino-aciduria. It may be of interest and value to compare urinary chromatographic patterns in the early and late phases and correlate them with white blood cell counts, bone marrow patterns, sedimentation rate, C-reactive protein, etc.

Amino-aciduria has been described in infants with kwashiorkor who were severely malnourished.[67] This amino-aciduria subsided with adequate diet. In our series two infants with severe infections, one with congenital toxoplasmosis and the other with a granulomatous lesion of the anterior mediastinum, also exhibited gross amino-aciduria.

Choremis et al.[68] described amino-aciduria in 13 of 16 patients during periods of active convulsions. This amino-aciduria decreased as seizures were controlled. Three of six patients in the present study exhibited gross amino-aciduria following seizures; this gradually returned to normal when seizures stopped or were controlled. All three had pneumoencephalographic evidence of cortical atrophy. Urinary alpha-amino nitrogen excretion in the other 3 patients was not greatly exaggerated even on the day of seizures. It is felt that amino-aciduria following convulsions is an effect of excessive muscle activity, stress, or alteration of brain metabolism.

Renal Amino-Aciduria (Normal Blood Level)—Congenital

Cystinosis (Lignac-Fanconi disease)[69–75] is characterized by growth retardation, rickets unresponsive to vitamin D, lethargy, anorexia and polyuria together with renal glycosuria, acidosis, hypokalemia, cystinuria, amino-aciduria and deposits of cystine crystals in body tissues, particularly the reticuloendothelial system. Diagnosis is confirmed by slit lamp examination of the cornea and by bone marrow and urine studies. Patients usually die before 16 years of age.[16] Many investigators feel the disease represents a recessively inherited error of cystine metabolism and is the infantile type of the Fanconi syndrome.[74, 75] Cystinosis can be differentiated from congenital renal tubular acidosis by the presence of cystine in the tissues.[71, 75] The triad of hypophosphatemia, phosphaturia, amino-aciduria and glycosuria is generally called the Fanconi syndrome.[70] Many of the diseases

mentioned in this discussion would therefore qualify as acquired renal tubular forms of this syndrome.

Dent and Harris[76] have described a syndrome of vitamin D-resistant rickets, osteomalacia, hyperglycinuria, elevated alkaline phosphatase, decreased serum bicarbonate, diminished renal phosphorus absorption and failure to grow after age twelve. Luder and Shelton[77] have reported the occurrence of a tubular defect in the absorption of amino acids and glucose in three generations of a family. One patient was small in stature. All glucose tolerance tests were normal.

Cystinuria is a condition in which cystine stones are present in the urinary tract; however, lysine is the amino acid excreted in abnormal amounts. Blood levels of cystine are normal, and loading studies have not shown any abnormality of the metabolism of sulfur-containing amino acids. There is no tissue deposition of cystine. Two phenotypes have been demonstrated by Harris and Robeson;[78] these may represent the homozygous and heterozygous form.

DeVries et al.[79] found excessive glycine excretion in four members of a family; three members had nephrolithiasis. A stone obtained from one of these patients contained a small amount of glycine in nonprotein, nonpeptide form. Failure to reabsorb glycine was not associated with defective reabsorption of other amino acids, glucose or phosphorus.

The primary metabolic defect in hepatolenticular degeneration (Wilson's disease) is felt to be due to a deficiency of ceruloplasmin which results in an increase of direct-reacting copper in the plasma, and, in time, in the tissues. This increased copper produces degeneration of the lenticular nuclei of the brain, cirrhosis of the liver, and Kayser-Fleischer rings in Descemet's membrane.[80-82] The metabolic error is due to an autosomal recessive gene.[82] The renal abnormality resulting in amino-aciduria is apparently toxic in nature since young infants with this condition have the ceruloplasmin deficiency but develop amino-aciduria at a later time. BAL[83] and penicillamine[84] are stated to increase copper excretion.

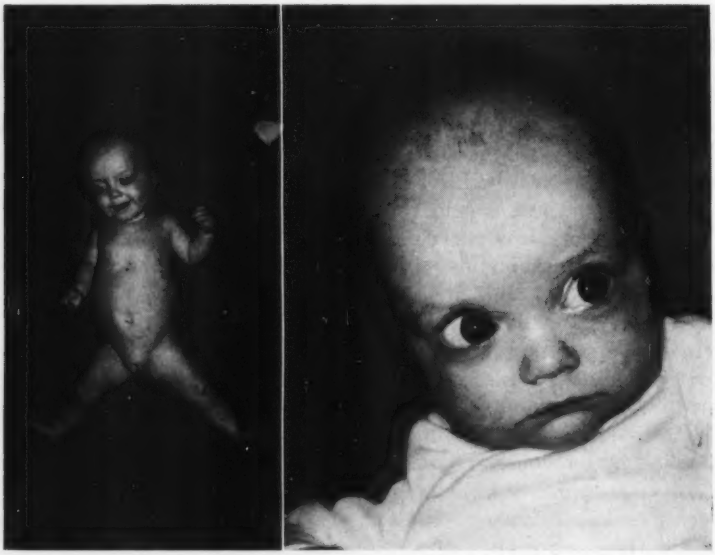
In patients with galactosemia, amino-aciduria is felt to represent a toxic renal tubular effect of galactose and its intermediary metabolites due to a deficiency of the enzyme, phospho-galactouridyl transferase.[82, 85] The disease frequently presents with feeding difficulty, diarrhea, cataracts, jaundice, convulsions, and edema. Diagnosis can be made by family history, the presence of galactosuria, determination of blood galactose level, galactose tolerance tests, and enzymatic assay.[18, 86, 87] Withdrawal of milk, and substitution of a low galactose diet results in cessation of galactosemia; if treatment is instituted in early infancy, disappearance of abnormal clinical findings occurs.[82]

Hartnup's disease[88, 89] is a familial disorder with pellagra-like skin rash,

photosenstitive skin, temporary periods of cerebellar ataxia, mental retardation, renal amino-aciduria and a disturbance in tryptophan metabolism indicated by the urinary excretion of indolacetic acid and other tryptophan metabolites. Nicotinic acid therapy may be beneficial in the acute episodes of the disorder.

Generalized amino-aciduria has been associated with many forms of mental deficiency.[20, 90] In this study there were 7 patients with mental deficiency who could not be placed in other categories and who did not show specific amino-acid patterns.

Lowe et al.[91] described a syndrome of mental retardation, hyporeflexia, flabby musculature, hydrophthalmos, cataracts, systemic acidosis, rickets or osteomalacia, organic-aciduria and amino-aciduria and decreased ability of the kidney to produce ammonia. The suggested treatment is added dietary base and vitamin D. Figure 7 (A and B) shows a female infant with hydrophthalmos, glaucoma, macrocephaly, hypotonia, and mental and physical retardation, who also had amino-aciduria. There is no evidence of consanguinity or family history of a similar disorder. Blood and urine studies failed to reveal acidosis or organic-aciduria. There was no x-ray



A B

FIG. 7 A. Female infant with hydrophthalmos, glaucoma, macrocephaly, hypotonia and physical and mental retardation accompanying amino-aciduria.

FIG. 7B. A close-up view of the head, showing macrocephaly and hydrophthalmos

evidence of rickets. It is felt that this patient represents a syndrome similar to that described by Lowe et al.; however, the patient does not show the same blood and urine findings. This infant will be reported in more complete detail.[22]

Numerous entities have been described in which amino-aciduria has occasionally been present. In this study patients with celiac syndrome and muscular dystrophy did not have the amino-aciduria reported by others.[92, 93] One patient with hypoplastic anemia and multiple congenital anomalies had anthranilic aciduria[94] but his alpha-amino nitrogen excretion was not excessive. Another patient who had had exchange transfusion for erythroblastosis showed an amino-aciduria which was not unusually elevated for his age.[95] As this study continues it is expected that the occurrence of amino-aciduria will be noted in further entities.

SUMMARY

The study of amino acids in the urine offers promise for the diagnosis, prognosis and treatment of disease. In the present series, urinary alpha-amino nitrogen excretion and amino-acid paper chromatography have been determined for 47 patients representing a spectrum of diseases and 8 normal controls. Patients with convulsive disorders, renal and hepatic disorders, accidental poisoning, failure to thrive, and neoplastic diseases largely constitute this study.

Amino-aciduria in salicylate intoxication is reported for the first time and a possible metabolic pathway for its occurrence is hypothesized.

An infant with a previously undescribed syndrome of macrocephaly, hydrophthalmos, glaucoma, hypotonia, mental and physical retardation and generalized amino-aciduria is presented.

It is suggested that similar studies be undertaken by others to evaluate specific excretion patterns of amino acids in disease processes in hope that new diagnostic methods, rational therapeutic approaches to management, and eventual understanding of metabolic pathways and mechanisms of drug action may become known.

ACKNOWLEDGEMENT

The author wishes to thank Colonel Ogden C. Bruton for his encouragement in this project, Colonel Tomas C. Jefferis and Lt. Col. Edward C. Knoblock for help with amino-acid determinations, and the Pediatric Nursing Service for the many hours spent in the collection of samples.

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Clinical Pathological Conference

Sydney Ross, M.D.*
Grace H. Guin, M.D.†

PRESENTATION OF CASE

This 8 week old white infant boy was admitted to Children's Hospital because of grunting respirations and colicky abdominal pains of 5 hours duration.

The patient had previously developed normally. He had suffered from a mild cold for about 10 days prior to admission, and on the evening prior to admission vomited once and began having grunting respirations and paroxysms of crampy abdominal pain. A small enema was unproductive. The infant became irritable and pale, and the grunting respirations and abdominal complaints continued.

On admission, the infant appeared to be a well developed, well nourished, pale and irritable 8 week old boy. Rectal temperature was 100.4°F. Occasional transmitted rhonchi were heard throughout the lungs. The abdomen was distended and apparently tender; an umbilical hernia which was easily reduced was also present.

On arrival, a barium enema was given, and roentgen examination revealed a redundant colon, but no obstruction of the small or large bowel.

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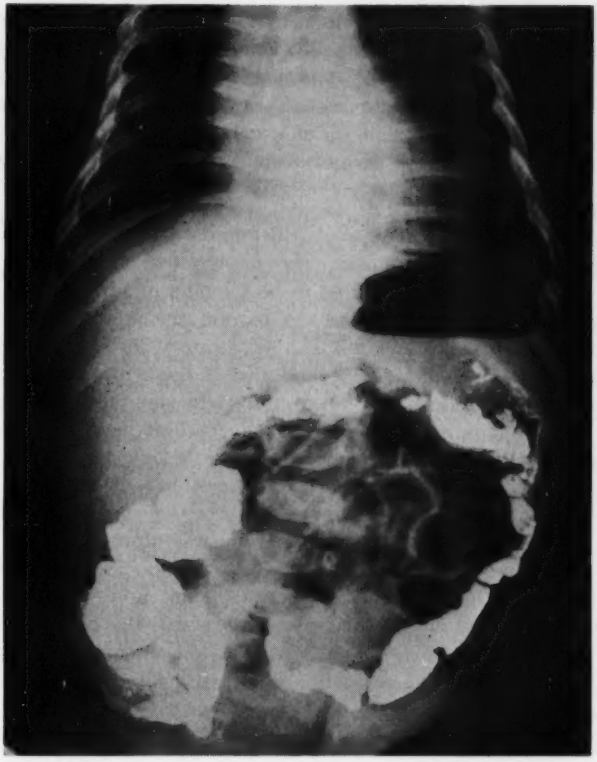

FIG. 1. Roentgenographic view of the abdomen and chest revealing barium distributed throughout the colon and a small amount in the distal ileum. There is no definite evidence of chest pathology although there is an early infiltrative lesion in the right cardiohepatic angle.

The enema was followed by expulsion of barium and some gas. Nine hours after admission x-ray examination of the abdomen revealed residual barium in the colon as well as dilated loops of small bowel which did not contain fluid levels (fig. 1). X-ray examination of the chest demonstrated no abnormality except for an early infiltration in the right cardiohepatic angle.

On admission, blood hemoglobin was 11 Gm. per 100 ml., hematocrit 37 per cent, leukocytes 10,000 per cu. mm., with 22 per cent segmented forms, 30 per cent bands, 43 per cent lymphocytes and 5 per cent monocytes. Platelets were adequate. Blood urea nitrogen was 20 mg. per 100 ml., and the carbon dioxide combining power 20.4 mEq. per liter.

Thirteen hours after admission an exploratory laparotomy was performed.

Postoperatively the infant continued having labored and grunting respirations. In the early morning of the following day, fine rales were heard in both lung fields. The infant's color became poorer and the cry weak, and he expired on the second hospital day 16 hours after surgery.

Dr. Ross:

In summary we have an 8 week old infant with sudden onset of paroxysmal colicky abdominal pain, who on physical examination demonstrated little except what appeared to be a tender abdomen with grunting respirations and a low grade fever. A barium enema was normal except for distended loops of small gut. An exploratory laparotomy was done 12 hours after admission, and the child died 16 hours after surgery.

Review of the x-rays in the prone and upright views illustrates some gas distended loops of bowel in the left abdomen; these most likely represent small bowel. The chest shows no evidence of pathology. Examination of the colon by means of a barium enema reveals the colon to be filled well without interference or delay; there was redundancy of the sigmoid and the distal portion of the descending colon. The barium was propelled into the ileum and there was no evidence of pathology in the region of the ileocecal valve. This represents a normal colon and distal ileum. Re-examination of the abdomen 15 hours after the barium enema reveals the barium to be distributed throughout the colon, a small amount remaining in the distal ileum. This is strongly suggestive of a normal colon and small intestine. Re-examination of the chest at this time demonstrated no definite evidence of pathology although there is an early infiltrate at the right cardiohepatic angle.

It probably would be worth while in discussing some of the diagnostic possibilities in this case to begin with the possible extra-abdominal causes of this infant's condition. The first diagnosis to be considered is sepsis. A small 2 month old infant with septicemia could conceivably present a picture of this sort; a fever of only 100.4°F. does not disturb us, because, as is well known, an infant with septicemia may have a normal or even subnormal temperature. An associated paralytic ileus, a condition which may accompany any severe infection, could account for the abdominal distention and the distended loops of small gut.

The possibility of a coexisting or pre-existing pneumonitis should be considered. This child had had a respiratory infection during the preceding 10 days and had some infiltration in the right cardiohepatic angle. We have seen children on the Diarrhea Ward, for example, who have been quite ill with a severe respiratory infection and have had extreme distention of the abdomen to the point where we were not quite sure whether the

child had indeed organic obstruction or merely severe ileus; more than one of these children have been examined in surgical consultation. Therefore, the mere presence of a remarkably distended abdomen should not preclude the possibility of an extra abdominal etiology.

An acute intestinal obstruction must be thought of, particularly in view of what was apparently acute persistent paroxysmal crampy abdominal pain. The first cause of acute intestinal obstruction that should come to mind in a 2 months old baby, even though the age group is not within the classical normal range, is an acute intussusception. Intussusception is common in the age group of 4 to 10 months, the onset is rather sudden, its pain is intermittent and colicky, vomiting oftentimes is present, and the classical currant-jelly stool may be absent. Gross[1] has indicated that currant-jelly stools may not manifest themselves until some 12 to 14 hours after the onset of this disease. The fact that no abdominal mass was palpated would give pause before considering the diagnosis too seriously, but again, 15 per cent of Gross's series had no palpable mass. Sometimes the mass may be small and be obscured by the liver, thus precluding adequate palpation. The fact that x-ray examination by barium enema was normal would certainly indicate the diagnosis should be considered less seriously. However, it should be pointed out that an ileoileal type of intussusception, which comprises about 5 to 8 per cent of all intussusceptions, may not illustrate any abnormal findings on x-ray.

Other causes of intestinal obstruction in a 2 months old baby should be considered. A midgut volvulus, duplication of a portion of the gut, or a fibrous band are all possibilities. We do not appear to be dealing with a complete obstruction, however. Vomiting was not conspicuous and there was no indication of any bile-stained vomitus; any obstruction, either partial or complete, below the ampulla of Vater generally would be accompanied by bile-stained vomitus. I do not think we can entertain very seriously these causes of intestinal obstruction.

Another cause of mechanical intestinal obstruction which should be mentioned in a 2 month old baby is congenital aganglionic megacolon. On occasion one may see a baby in this age group with a distended abdomen, oftentimes accompanied by constipation, but sometimes with a presenting symptom of diarrhea, who has been diagnosed subsequently to have aganglionic megacolon. The x-rays in the present case again add no credence to this possibility; there is no narrowing of the terminal portion of the rectosigmoid with a proximal dilatation of the bowel above the aganglionic area.

A more likely possiblity in this infant is peritonitis. Peritoneal disease which might be encountered in this age group may be divided arbitrarily into two groups: primary peritonitis, and secondary peritonitis due to ruptured viscus. The diagnosis of primary peritonitis oftentimes is ex-

tremely difficult in a 2 month old baby, and is often made initially at postmortem. Generally, primary peritonitis is due either to hemolytic streptococcus or pneumococcus; it is not so common as it was prior to the advent of antibiotic therapy. It is sudden in onset, and while in older children it may present a more compelling picture, in a small baby it may only present a picture of abdominal pain and irritability with or without fever. Even though the absence of fever in a 2 month old baby is not a very reliable index as to the severity of any given entity, this infant might have had a higher white blood cell count than he did. In the cases of primary peritonitis which I have seen, white blood counts have ranged from 20,000 to 40,000 per cu. mm. However, one cannot exclude a diagnosis of a primary peritonitis in this baby, particularly in view of the fact that he had a preexisting respiratory infection and early pneumonitis. The possibility of a resulting septicemia and seeding into the peritoneal cavity is worthy of note.

The secondary type of peritonitis due to ruptured viscus should certainly be entertained in this child. There are several varieties. There is the so-called spontaneous perforation of the stomach wall due to a defect in the musculature of the stomach; several cases have been recorded where there has been a sizeable rent in the gastric musculature with spilling of gastric contents into the peritoneal cavity and resulting chemical peritonitis. Another cause is peptic ulcer. Although one does not usually think of peptic ulcer in a 2 month old baby, they have been reported. Gross has reported ruptured peptic ulcer in a 3 day old baby. A third cause of a ruptured viscus is the Rokitansky-Cushing ulcer. We have seen these, particularly in the child with severe gastroenteritis who suddenly starts to vomit blood and passes melena in the stool. Against a diagnosis of peritonitis secondary to ruptured viscus, however, is the absence of pneumoperitoneum, a finding which generally is regarded as pathognomonic for this entity.

In summary, my first choice is primary peritonitis; secondary peritonitis following a ruptured viscus would certainly have to be considered. My second choice is ileoileal intussusception. The child probably had, in addition, a coexisting pneumonitis.

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Dr. Guin:

At the time of surgery, the only positive finding was the presence of enlarged mesenteric lymph nodes. Microscopically this enlargement reflected hypertrophied lymphoid tissue, and, in addition, there was focal acute enteritis which had not been visible grossly. The surgeon made a

note that there was a thin, small congenital band in the region of the cecum, but in his opinion this did not play any significant role as there was no evidence of obstruction.

At autopsy an extensive staphylococcal pneumonia with abscess formation was noted. Masses of bacteria were visible in some of the areas of vessel wall erosion. The right pleural cavity contained 30 ml. of turbid straw colored fluid. Cultures taken at autopsy from this fluid, blood and lung revealed hemolytic *Staphylococcus aureus*. The last chest x-rays indicate that an infiltrative process of some sort was present. It is regrettable that the nature of the infiltrative process was not known prior to surgery.

Dr. Ross:

This case exemplifies several points extremely well. First, the fact that in spite of the infant's overwhelming staphylococcal pneumonia his temperature was only very slightly elevated; this again illustrates that severe infections may occur with normal temperatures. Second, that infections as severe as staphylococcal pneumonia may occur in the absence of marked leukocytosis. Third, that an illness such as this, initially low grade and smoldering, and then suddenly increasing in severity in rapid fashion may indicate the presence of an 80–81 phage type staphylococcus. And fourth, that blood cultures should be taken with more frequent regularity in obviously acutely ill infants, even though there seems to be no indication from the results of the physical examination.

Panel Symposium: The Pediatrician's Role in the Team Approach to the Child who Goes to School

WILLIAM J. PEEPLES, M.D.*
BELINDA STRAIGHT, M.D.†
MARY ALICE V. FOX, M.D.‡

Dr. Peeples:

A school health program is indispensable to public health, first, because it provides a service needed in the community, and second, because it pro-

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vides an educational experience for not only the child but for teachers, nurses and, frequently, physicians in the community. School health services have changed a great deal in the last few years in that there has been less emphasis toward the physical and more toward the emotional aspect of the child's health. Most physical defects in the present era are being corrected before the child becomes of school age. In general, there has been increasingly greater emphasis in school systems toward special education of the child with various learning handicaps such as specific reading disability and specific speech disability.

We see our role as a health department providing a school health service in several lights. One is that we do not want to interfere in any way with the private practice of medicine; on the other hand, the attitudes of the health department can enhance, stimulate and act as a catalyst to the private practice of medicine. Second, we have certain legal responsibilities with regard to communicable disease which by law we cannot escape. Third, we have a responsibility for communicating to the community certain aspects of school health which we feel are important. Fourth, we need to work with school authorities in a cooperative effort to provide them with medical consultation to the problems of education.

A school health program cannot be conducted alone by the Health Department; the efforts of everyone in the community are necessary to do this effectively. We see the pediatrician in the community particularly as a coordinator. In this capacity he can provide the proper medical consultation and also often be very helpful in interpreting the reasons for physical and emotional aberrations to school authorities.

The pediatrician interested in school health problems, in addition, can act as liaison between the private physician in the community, the health department, and the school system. This pediatrician we call our "school medical advisor." As an example, a school medical advisor recently discovered a child who had been in speech therapy classes for a number of years; this child had continued to be somewhat of a problem in school and was observed by the physician in Latin class. The child had a very definite speech defect which sounded as though there were some type of nasal obstruction. Even though this was a child who had received quite satisfactory previous medical supervision, he was referred for otolaryngology consultation which disclosed a nasal polyp and some folding over of the uvula. Both these defects were corrected and the child is no longer in speech class.

In another instance, a child had been placed on limited physical activity by his private physician and had not been allowed to participate in the physical education program. The school medical advisor reviewed all the medical information and talked with the private pediatrician; together

they decided the child might have an incipient collagen disease. A trial of oral penicillin was begun and continued for two months; all symptoms disappeared and the child is now taking physical education. No definite diagnosis was made, but the child is now functioning well.

Dr. Straight:

September and June are the two times a year when the pediatrician receives distress calls from parents for their child's school problem. In June it is, "Why didn't he pass?" and in September it is, "How can I get him to go to school?"

In a discussion of reluctance to go to school, we must first differentiate between the normal reluctance that many children feel about entering school for the first time in the fall, and the more malignant and serious problem of chronic avoidance of school, or acute school phobia. The Elizabethans were quite aware of this reluctance to go to school. Shakespeare, in "As You Like It," described "The schoolboy with his sachel and shining face creeping like a snail unwillingly to school." Most children, however, get over this phase. This is for two reasons: one is that the parents are able to communicate to the child their calm expectation he is going back to school and will find satisfactions there; the second consists of the actual satisfaction of school life and friends, and the pleasure in learning and mastering. These reasons are usually enough to give the child impetus to return to school.

However, the reluctance to go to school can become a chronic problem, and we see cases of mild anorexia and diarrhea, headaches, etc. The problem then becomes, "What do you do about it?" The one thing we know is that the longer the child stays away from school the more difficult it becomes for him to return. This has been termed "school phobia." We know that school phobia is not fear of going to school, but instead reluctance of the mother to let her child separate from her and reluctance of the child to separate. This is an important distinction between truancy and school phobia, because the truant child, when he doesn't go to school, is willing to go off somewhere else, whether fishing or looking in shop windows, etc.

Sometimes the pediatrician becomes an unwitting co-conspirator in keeping the child home from school. He can do this by writing out attendance excuses even though he is reasonably certain that the child has no serious physical problem. In this way he can provide the mother and child a basis for prolonged fear which will secondarily make it more difficult for the child to return to school.

What can be done once school phobia has set in? If the anxiety is fairly acute, our main concern is to get the child back to school immediately, if

only to have him sit for a short period in the counselor's office or pick up his homework. Actual physical contact with the school is important. This can sometimes be aided by giving tranquilizing drugs, but if the problem persists or worsens, a psychiatrist should be consulted.

We can sometimes predict which child will have school phobia by looking for the child in office practice who has persistent separation anxiety. The separation problem then can be worked on long before the child actually reaches school. This can be done in several ways. One way is by using anticipatory guidance directed toward the problems of separating and how these can be handled. The father particularly should be brought in on the planning, since we know that traditionally fathers of children with school phobias tend to withdraw themselves from the problem. The second preventive measure the pediatrician may use is to ask the parents to have the nursery school send school reports of the child's participation to him, because these also give clues as to which child is going to have trouble.

In addition, the pediatrician can include in his examination a routine question about absence from school since it is often found that a mother will keep her child home from school but won't call the pediatrician. She will keep him home because it is too cold, or because he looks pale, or because he might be getting a stomach-ache. Consequently, a routine question on actual school attendance of the child will alert the physician to possible difficulty.

Another area of difficulty concerns reading problems. We know that reading problems account for most school failures and that most reading problems come to light if looked for carefully by the end of the first grade. It is estimated that about 30 per cent of children have or have had reading problems. Many of these children may have a "developmental lag" which may be discovered by using reading readiness tests. These handicaps can be overcome, but again are made worse by superimposed emotional problems with which the child has to cope at the same time. Again, the recognition of a child who is beginning to have difficulty in the school allows one time enough to begin to work on his problems before they have become too set, whether it be by pediatric counseling of parents, through special school services for children, or by child guidance clinics.

Children play "hookey" for different reasons. There is the Huck Finn-Tom Sawyer type of truant who goes off to have a good time. There is the truant who runs off because he is afraid of punishment for not being able to accomplish. There is the truant who has a problem in reading and cannot face failure. Perhaps the most common cause of truancy is "out-of-control" behavior. Truancy is only one indication that this particular child is out of control. Again one gets early indications in office practice of which children and which parents are apt to engender this problem. Some-

times these are the children with hyperactive behavior for whom limits are not being set by the parents. Reports from the school during the first years of school life often are worth studying as important laboratory data. It is possible to predict to some extent which children will have trouble in adolescence.

In general, with all these problems, early detection is necessary and frequently possible, if not in office practice then from early school records. Most can be handled very well by the pediatrician; some may need referral to the psychiatrist or other specialized services.

Dr. Fox:

It is quite difficult for a pediatrician in full time private practice to be all that the school medical advisor would like him to be. It takes more time than the average pediatrician has available to settle school problems over the telephone or in face-to-face discussions with the parent and teacher, or with other school personnel.

The first official contact between the pediatrician and the school occurs when the child who is entering the first grade is required to have a school health form completed. This becomes somewhat routine, but there are a few lines on the school health form which can help both the child and the school if only they are filled out with half a minute's thought. These refer to the question (and most school systems have a question equivalent to this), "What can be done to help the teachers help the child benefit from his school experience?" If the pediatrician would indicate in the appropriate case that there is something that can be done, or if he would just say, "I will be glad to discuss this with the teacher," instead of leaving it blank with no comment at all, a good deal could be accomplished.

The pediatrician can discuss school progress with the mother. "What does he like about school?" Many parents feel that school problems are the school's concern, and that health problems are the pediatrician's concern. Questions concerning school progress tell the mother that the pediatrician is interested and possibly able to help work out the school problems (if there are any). A recent school problem was inadvertently solved because the father inquired from the physician how to get a psychological test for his child who was not learning to read in the first grade. When asked whether he had talked with the teacher concerning the problem, he said, "Oh no, I hadn't thought about that." Neither this father nor mother had been in to talk about their child's progress, and only a face to face conference between parents and teacher was needed to solve what was merely delayed learning in an otherwise normal child.

If a school problem presents itself, the next thing the pediatrician can do is to follow through by calling the school nurse or the teacher. Both parents

and teacher can then feel much more relaxed because the pediatrician becomes the neutral ground on which both can give vent to their feelings. Such a simple maneuver may avert a serious problem.

Not the least important role a pediatrician plays is in instructing the child in health rules, such as toilet cleanliness, brushing teeth, etc.

If the pediatrician has put this relatively minor effort into helping his patient in school, the school can, in turn, help him with the child. The child who comes into his office is only one little facet of the whole child who lives, eats and sleeps, and goes to school; the pediatrician sees this child usually on his best behavior and in a very isolated setting. The child behaves quite differently in a group of children from the way he behaves in the pediatrician's office with only adults observing him. The school teacher can provide the pediatrician with information concerning symptoms which the child presents in a group which are inconspicuous to parent or physician. Sometimes these symptoms may be diagnostic. Hyperactive behavior sometimes can be a clue to a diagnosis. In one child who had chorea, the teacher was the individual who first noted this behavior, since in a group of normal children the choreiform movements were eye-catching. Neither the parents (who had a family of four children) nor the pediatrician in his office had noticed the unusual activity in this child because it was not that marked. It is frequently possible that an astute teacher can provide information of considerable use to help both physician and parent to guide the child to better physical and emotional health.

Book Review

Blood Diseases of Infancy and Childhood. By CARL H. SMITH, M.D., 572 pages, 51 illustrations, St. Louis: The C. V. Mosby Company, 1960, $17.00.

This book is an excellent, timely textbook on the rapidly growing subject of pediatric hematology. It will be useful to both the generalist and pediatrician as a library or laboratory shelf reference. Discussions of such basic principles as the origin and development of blood cells and the blood changes during pediatric growth and development are invaluable, as are the charts listing the normal variants for the different age groups. The chapters on basic hemolytic principles, and blood groups and transfusions in pediatric practice will be an excellent source of reference to the busy practitioner, enabling him to locate important facts quickly during a

busy pediatric day. Modern concepts of diagnosis and treatment and identification of the important pediatric hematological problems are well covered. There is a wide range of subject matter including neonatal jaundice, iron deficiency anemia, hemolytic anemia and severe disease entities such as leukemia. The book is written in such a way that it is extremely easy to read. It is comparatively simple to arrive at the meat of a problem rapidly.

Dr. Smith has also taken a good deal of time to incorporate excellent photographs in appropriate places to bring to the reader a visual impression of the conditions he is describing.

All in all this book is highly recommended as an important tool in the office or laboratory of all physicians conscientiously interested in the care of infants and children.

DAN FERIOZI, M.D.

Index to Volume 17

AUTHORS INDEX*

* January, pp. 1–30; February, pp. 31–58; March, pp. 59–90; April, pp. 91–122; May, pp. 123–144; June, pp. 145–170; July, pp. 171–194; August, pp. 195–218; September, pp. 219–242; October, pp. 243–262; November, pp. 263–290; December, pp. 291–333.

SUBJECT INDEX*

* January, pp. 1–30; February, pp. 31–58; March, pp. 59–90; April, pp. 91–122; May, pp. 123–144; June, pp. 145–170; July, pp. 171–194; August, pp. 195–218; September, pp. 219–242; October, pp. 243–262; November, pp. 263–290; December, pp. 291–333.

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